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| (54) Title: MEDICINAL AEROSOL FORMULATIONS (57) Abstract <p>A self-propelling, powder dispensing aerosol composition comprising at least 0.0001 % by weight of a finely-divided solid medicament coated with a non-perfluorinated surface-active dispersing agent which constitutes at least 0.0001 % by weight of the coated solid material, and suspended in an aerosol propellant in which the non-perfluorinated surface-active dispersing agent is substantially insoluble. Non-fluorinated surfactants which are insoluble in propellants, such as Propellant 134a, may be used to prepare stable dispersions of powdered medicament provided the medicament is pre-coated with the surfactant prior to admixture with propellant.</p> | | |

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MEDICINAL AEROSOL FORMULATIONS

This invention relates to medicinal aerosol formulations and in particular to formulations suitable for pulmonary, nasal, buccal or topical administration
5 which are at least substantially free of chlorofluorocarbons.

Since the metered dose pressurised inhaler was introduced in the mid 1950's, inhalation has become the most widely used route for delivering bronchodilator
10 drugs and steroids to the airways of asthmatic patients. Compared with oral administration of bronchodilators, inhalation offers a rapid onset of action and a low instance of systemic side effects. More recently, inhalation from a pressurised inhaler has been a route
15 selected for the administration of other drugs, e.g., ergotamine, which are not primarily concerned with the treatment of a bronchial malady.

The metered dose inhaler is dependent upon the propulsive force of a propellant system used in its
20 manufacture. The propellant generally comprises a mixture of liquified chlorofluorocarbons (CFC's) which are selected to provide both the desired vapour pressure and stability of formulation. Propellants 11, 12 and 114 are the most widely used propellants in aerosol
25 formulations for inhalation administration.

In recent years it has been established that CFC's react with the ozone layer around the earth and contribute towards its depletion. There has been considerable pressure around the world to reduce
30 substantially the use of CFC's, and various Governments have banned the "non-essential" use of CFC's. Such "non-essential" uses include the use of CFC's as refrigerants and blowing agents, but heretofore the use of CFC's in medicines, which contributes to less than 1% of the total
35 use of CFC's, has not been restricted. Nevertheless, in view of the adverse effect of CFC's on the ozone layer it is desirable to seek alternative propellant systems which are suitable for use in inhalation aerosols.

Our copending European Patent Application No. 89312270.5 discloses an aerosol formulation comprising a medicament, a surfactant, 1,1,1,2-tetrafluoroethane and at least one compound having a higher polarity than 1,1,1,2-tetrafluoroethane.

It is disclosed that 1,1,1,2-tetrafluoroethane, hereinafter referred to as Propellant 134a, may be employed as a propellant for aerosol formulations suitable for inhalation therapy when used in combination with a compound having a higher polarity than Propellant 134a. Suitable compounds include alcohols such as ethyl alcohol, isopropyl alcohol, propylene glycol, hydrocarbons such as propane, butane, isobutane, pentane, isopentane, neopentane, and other propellants such as those commonly referred to as Propellants 11, 12, 114, 113, 22, 142b, 152a, 124 and dimethyl ether. The combination of one or more of such compounds with Propellant 134a provides a propellant system which has comparable properties to those of propellant systems based on CFC's, allowing use of known surfactants and additives in the pharmaceutical formulations and conventional valve components. This is particularly advantageous since the toxicity and use of such compounds in metered dose inhalers for drug delivery to the human respiratory tract is well established.

Non-perfluorinated surfactants have commonly been used as dispersing agents for powdered medicaments in aerosol propellants in which the non-perfluorinated surfactants are soluble. Examples of such aerosol formulations are disclosed in British Patents Nos. 837465, 977934, 1063512, 2001334 and US Patent No. 4352789. However, many of these non-perfluorinated surfactants are substantially insoluble in Propellant 134a and other propellants which are being considered as replacements for chlorofluorocarbon aerosol propellants i.e., at an ordinary room temperature it requires more than 10,000 parts of propellant to dissolve 1 part of surfactant.

It has been found that non-perfluorinated surfactants which are insoluble in a propellant may nevertheless be used with such a propellant to form stable dispersions of powdered medicament provided the powdered medicament is pre-coated with the non-perfluorinated surfactant prior to dispersing the powdered medicament in the propellant.

Therefore according to the invention there is provided a self-propelling, powder dispensing aerosol composition comprising at least 0.001% by weight of a finely-divided solid medicament coated with a non-perfluorinated surface-active dispersing agent which constitutes from 0.001 to 20% by weight of the coated solid medicament, and suspended in an aerosol propellant in which the non-perfluorinated surface-active dispersing agent is substantially insoluble.

It has been found that non-perfluorinated surfactants, which have previously been used as dispensing agents for powdered medicaments in propellants in which the non-perfluorinated surfactant is soluble, may be used to form stable dispersions of powdered medicament in propellants in which the non-perfluorinated surfactant is insoluble provided the medicament is pre-coated with the surfactant prior to dispensing in the propellant. This result is particularly surprising in view of the fact that the same stable dispersions cannot be achieved by simple admixture of the surfactant, propellant and medicament.

The invention is particularly useful in that it allows acceptably stable dispersions to be attained using Propellant 134a as the aerosol propellant. The formulations of the invention may be prepared with Propellant 134a alone or a mixture of Propellant 134a and another miscible adjuvant having a polarity equal to or lower than the polarity of Propellant 134a. Suitable adjuvants for use with Propellants 134a include perfluorinated organic compounds such as perfluorinated alkanes and cycloalkanes. Specific examples of adjuvants include those shown in the following Table

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